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Immunohistochemical Evaluation of Ki-67 and PTEN Expression in Endometrial Adenocarcinoma: Correlation with Histological Grade and Prognostic Implications

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Abstract

Background: Endometrial adenocarcinoma is among the most common gynecologic cancers in the world and with rising incidence which can be attributed to obesity, type 2 diabetes mellitus and lifetime exposure to unopposed estrogen. Traditional prognostic factors (histological grade and FIGO stage) are not sufficient to describe the molecular heterogeneity of this tumor. Ki-67 is a nuclear proliferation biomarker expressed at all active cell-cycle phases and PTEN is the most commonly inactivated tumor suppressor in endometrioid carcinoma, whose joint evaluation could provide better prognostic stratification.

Objective: To examine the Ki-67 and PTEN immunohistochemistry in endometrial adenocarcinoma, correlate the expression of both biomarkers with histological grade and test the statistical correlation between the two biomarkers as composite prognostic factors.

Materials and Methods: The data was analyzed in terms of grading (by hematoxylin and eosin (H&E) staining) according to WHO 2020s classification and immunohistochemistry (Ki-67 (labeling index scored 0 to 4+, measured in 5 high-power fields) and PTEN (immunoreactive score 0 to 9: absent, low, moderate, or high) of 50 formalin-fixed paraffin-embedded (FFPE) endometrial adenocarc Chi-square test and Spearman rank correlation coefficient (significance level: $p < 0.05$) were used to evaluate the statistical associations.

Results: The high level of Ki-67 (>51%), moderate level (12), and low level of Ki-67 (8) were observed in 30 cases (60%), 12 cases, and 8 cases respectively. In 25 cases (50%), PTEN was absent altogether (25); in 15 cases (30%), it was low, in 8 cases (16%), it was moderate, and in 2 cases only (4%), it was high. Cross-tabulation showed that complete PTEN loss was seen in 66.7% of high-Ki-67. An important negative correlation was established between the two markers (2 = 17.91, 6df = 6, p = 0.0065; Spearman 0467, p = 0.0006).

Conclusion: Ki-67 and PTEN are valid and complementary immunohistochemical biomarkers to use in assessing tumor aggressiveness in endometrial adenocarcinoma. Their high negative correlation is an indicator of PI3K/AKT/mTOR pathways deregulation as a result of PTEN loss. Combined assessment enhances prognostic risk stratification, contributes to the targeted making of therapeutic decisions, and should be validated by using larger multicenter prospective studies.

Keywords: *Endometrial adenocarcinoma; Ki-67; PTEN; Immunohistochemistry; Tumor suppressor; Prognostic biomarkers; PI3K/AKT/mTOR*

Introduction

The most prevalent gynecologic malignancy in the developed world and the fourth most prevalent cancer in every part of the world is endometrial adenocarcinoma. It is becoming more and more common in association with the growing obesity, type 2 diabetes mellitus, and long periods of unopposed exposure to estrogen (Creasman, 2009; Morice et al., 2016). The disease is traditionally divided into two biological types: Type I (endometrioid, estrogen-dependent, usually of low grade, with favorable prognosis) and Type II (non-endometrioid, including serous (as well as clear-cell and carcinosarcoma) types, which behave aggressively and have a poor prognosis) (Bosse et al., 2015; WHO Classification of Tumours Editorial Board, 2020).

PTEN, (Phosphatase and Tensin Homolog) is a negative regulator of the PI3K/AKT/mTOR signaling pathway that is located in chromosome 10q23.3. It is the most commonly mutated tumor suppressor in endometrioid adenocarcinoma, inactivation of which is observed in 40 -83 percent of cases (Zhao et al., 2013; Pallares et al., 2005). PTEN loss facilitates constitutive AKT signalling leading to unrestrained cell survival, fast growth and apoptotic resistance -characteristic of malignant transformation (Zhao et al., 2013; Pallares et al., 2005).

Ki-67 is a nuclear protein with a transcript present in all cells in all active cell cycle phases (G1, S, G2 and M), but not in quiescent G0 cells, which is a universal and clinically validated proliferation marker. High levels of Ki-67 labelling have always been linked to high histological grade, lymphovascular invasion, and poor survival in endometrial carcinoma (Zhao et al., 2013; Pallares et al., 2005).PTEN and Ki-67 provide mechanically complementary data: deregulated tumor suppression is seen in loss of PTEN, and the resulting proliferative response is measured by Ki-67.

Although the individual prognostic value of these biomarkers has been firmly established, data on their combined immunohistochemical analysis in groups of patients in Iraq has not been properly examined. The current research was structured to describe the immunohistochemical phenotype of Ki-67 and PTEN in a case of 50 endometrial adenocarcinoma and to match their expression with histological grade and the systematic evaluation of their prognostic complementarity.

Materials and methods

2.1 Study Design and Sample Collection

This retrospective cross-sectional study was approved by the Institutional Review Board of the University of Sumer / Al-Karameh Teaching Hospital, Wasit Province, Iraq (Approval No.: 198587-2025) and was conducted in accordance with the principles of the Declaration of Helsinki. Fifty FFPE endometrial adenocarcinoma tissue blocks from women aged 18–80 years attending hospitals in Al-Kut City, Iraq,

were included. Demographic and clinical data were systematically documented for all patients. Cases with inadequate tissue preservation, prior radiotherapy, or concurrent malignancies were excluded.

2.2 Histopathological Examination

Serial sections (4 µm) were cut from each FFPE block and stained with hematoxylin and eosin (H&E) for histological diagnosis and grading (Bancroft & Gamble, 2013). Tumors were graded according to the WHO 2020 Classification of Female Genital Tumours (Mutter & Ferenczy, 2002). All cases were independently reviewed by two board-certified pathologists; discrepancies were resolved by consensus.

2.3 Immunohistochemistry Protocol

Heat-induced epitope retrieval (HIER) was performed using citrate buffer (pH 6.0, 95°C, 15 min) for Ki-67 and Tris-EDTA buffer (pH 9.0, 95°C, 20 min) for PTEN. Primary antibodies were applied overnight at 4°C: anti-Ki-67 (clone MIB-1, 1:100 dilution) and rabbit monoclonal anti-PTEN (1:100 dilution). Detection was performed using a horseradish peroxidase (HRP)-conjugated secondary antibody system with 3,3′-diaminobenzidine (DAB) chromogen, followed by hematoxylin counterstaining (Taylor et al., 2019; Kitson et al., 2018).

2.4 Immunohistochemical Scoring

The Ki-67 Labeling Index (LI) was defined as the percentage of immunoreactive tumor nuclei among a minimum of 500 tumor cells counted across five representative high-power fields (HPFs, ×400). Scoring categories are presented in Table 1. The PTEN Immunoreactive Score (IRS) was calculated as the product of staining intensity (0 = absent, 1 = weak, 2 = moderate, 3 = strong) and the proportion of positive cells (0 = 0%, 1 = 1–33%, 2 = 34–66%, 3 = 67–100%), yielding a range of 0–9, classified as: absent (IRS = 0), low (IRS 1–3), moderate (IRS 4–6), or high (IRS 7–9) (Urruticoechea et al., 2005; Mutter et al., 2001; Hussain et al., 2018).

Table 1. Ki-67 Labeling Index Scoring Categories

Score	% Positive Nuclei	Category
0	< 5%	Negative / Very Low
1+	5–25%	Low
2+	26–50%	Moderate
3+	51–75%	High
4+	> 75%	Very High

LI = Labeling Index. Scoring performed across ≥500 tumor cells in five high-power fields (×400).

2.5 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Categorical associations between Ki-67 and PTEN expression categories and histological grade were evaluated using the Chi-square test or Fisher's exact test, as appropriate. The correlation between Ki-67 LI and PTEN IRS was assessed by Spearman's rank correlation coefficient (ρ). Binary logistic regression was used to identify independent predictors of high Ki-67 expression. A p-value < 0.05 was considered statistically significant.

Results

3.1 Patient Characteristics

The study cohort comprised 50 women with a mean age of 59.0 ± 12.8 years (range: 28–78 years). On histopathological grading, Grade 1 tumors were identified in 5 cases (10%), Grade 2 in 28 cases (56%), and Grade 3 in 17 cases (34%). Patient demographics and tumor characteristics stratified by histological grade are presented in Table 2. Mean Ki-67 LI increased progressively from Grade 1 to Grade 3, while mean PTEN IRS demonstrated a corresponding decline, consistent with the expected inverse relationship between proliferative activity and tumor suppressor expression.

Table 2. Patient Demographics and Tumor Characteristics Stratified by Histological Grade

Variable	Grade 1	Grade 2	Grade 3	p-value
n (%)	5 (10%)	28 (56%)	17 (34%)	—
Age (years)	52.4±8.2	58.6±11.3	63.1±9.7	0.038*
Ki-67 LI (%)	28.5±6.1	55.3±12.4	74.2±10.8	0.001**
PTEN IRS	5.2±1.1	2.8±1.6	0.6±0.9	0.001**

*Values = mean ± SD or n (%). *p < 0.05; **p < 0.01 (One-way ANOVA or Kruskal–Wallis test, as appropriate). LI = Labeling Index; IRS = Immunoreactive Score.*

3.2 Ki-67 Expression

Ki-67 labeling indices across the cohort ranged from 8% to 92%. High expression (>51%) was recorded in 30 cases (60%), moderate expression (26–50%) in 12 cases (24%), and low expression (<25%) in 8 cases (16%) (Table 3). A progressive increase in mean Ki-67 LI was observed with advancing tumor grade (Grade 1: 28.5%; Grade 2: 55.3%; Grade 3: 74.2%), as illustrated in Figure 3B. The frequency distribution of Ki-67 LI across all 50 cases is depicted in Figure 3A.

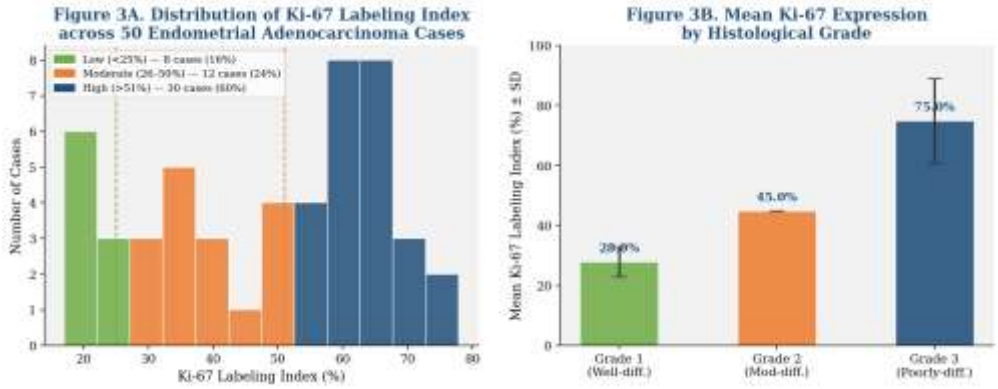

Fig. 3. (A) Histogram of Ki-67 labeling index (LI) distribution across 50 endometrial adenocarcinoma cases. Color-coded categories: green = Low (<25%), orange = Moderate (26–50%), blue = High (>51%). (B) Bar chart depicting mean Ki-67 LI (± SD) stratified by histological grade, illustrating a progressive increase in proliferative activity with tumor de-differentiation.

3.3 PTEN Expression Profile

PTEN expression was completely absent (IRS = 0) in 25 cases (50%), low (IRS 1–3) in 15 (30%), moderate (IRS 4–6) in 8 (16%), and high (IRS 7–9) in only 2 (4%) (Table 3). Overall, 80% of cases

demonstrated absent or low PTEN expression. Figure 4A presents the proportional distribution of PTEN expression categories, while Figure 4B illustrates the predominance of absent or low PTEN in high Ki-67 cases.

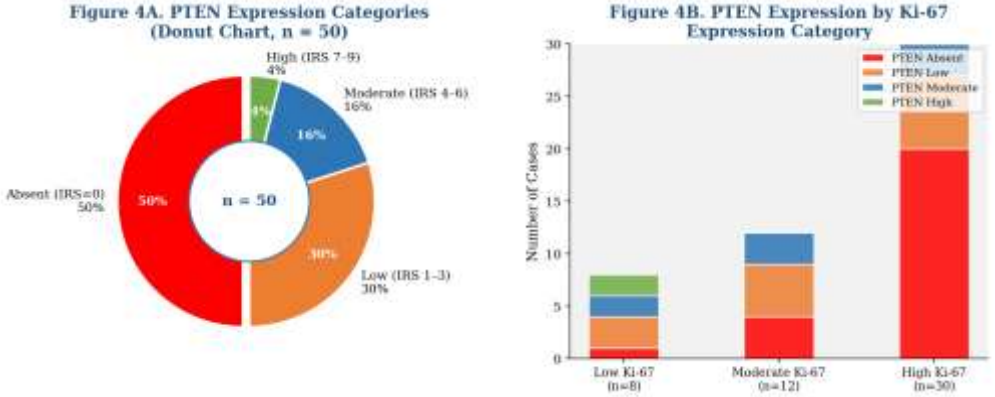

Fig. 4. (A) Donut chart showing the proportional distribution of PTEN expression categories (IRS-based) in 50 endometrial adenocarcinoma cases. (B) Stacked bar chart depicting PTEN expression levels across Ki-67 expression categories, highlighting the inverse relationship between the two biomarkers.

Table 3. Distribution of Ki-67 and PTEN Expression Levels in 50 Cases

Marker	Expression Category	n	% of Cases
Ki-67	High (>51%)	30	60.0%
	Moderate (26–50%)	12	24.0%
	Low (<25%)	8	16.0%
PTEN	Absent (IRS = 0)	25	50.0%
	Low (IRS 1–3)	15	30.0%
	Moderate (IRS 4–6)	8	16.0%
	High (IRS 7–9)	2	4.0%

Ki-67 LI = Labeling Index; PTEN IRS = Immunoreactive Score. Scoring criteria detailed in Section 2.4.

3.4 Correlation Analysis

Cross-tabulation of Ki-67 and PTEN expression categories (Table 4) demonstrated a clear inverse distribution: 20 of 30 high-Ki-67 cases (66.7%) exhibited complete PTEN loss, while low-Ki-67 cases were predominantly associated with moderate or high PTEN expression. A statistically significant association was confirmed by Chi-square analysis ($\chi^2 = 17.91$, df = 6, $p = 0.0065$), and a moderate-to-strong negative correlation was established by Spearman's rank test ($\rho = -0.467$, $p = 0.0006$) (Table 5). This inverse relationship is further illustrated by the scatter plot with regression trend line (Fig. 5) and the intensity heatmap (Fig. 6).

Table 4. Cross-Tabulation of Ki-67 × PTEN Expression (n = 50)

Ki-67 \ PTEN →	Absent	Low	Moderate	High	Total
High Ki-67	20 (40%)	7 (14%)	3 (6%)	0 (0%)	30
Moderate Ki-67	4 (8%)	5 (10%)	3 (6%)	0 (0%)	12
Low Ki-67	1 (2%)	3 (6%)	2 (4%)	2 (4%)	8
Column Total	25 (50%)	15 (30%)	8 (16%)	2 (4%)	50

Values represent n (% of total cohort). Row totals indicate absolute case counts per Ki-67 category.

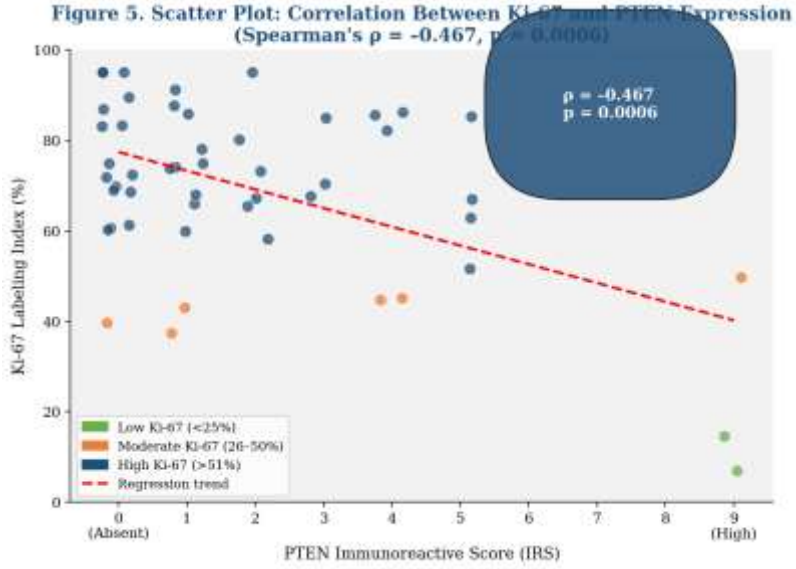

Fig. 5. Scatter plot depicting the inverse correlation between PTEN Immunoreactive Score (IRS) and Ki-67 Labeling Index (%) across 50 cases. Data points are color-coded by Ki-67 expression category. The dashed regression line confirms the significant negative trend (Spearman's ρ = −0.467, p = 0.0006).

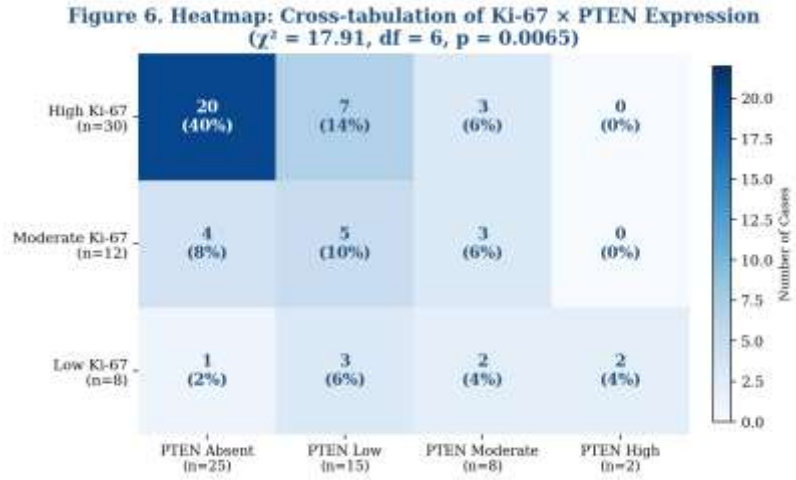

Fig. 6. Heatmap illustrating the cross-tabulation of Ki-67 × PTEN expression categories. Color intensity (blue gradient) reflects case counts; numerals indicate n and % per cell. The upper-left quadrant (High Ki-67 / PTEN Absent) dominates (40% of all cases), visually confirming the significant inverse association (χ² = 17.91, p = 0.0065).

Table 5. Statistical Evaluation of Ki-67 vs. PTEN Correlation

Statistical Test	Value	df	p-value
Chi-square (χ^2)	17.91	6	0.0065*
Spearman's correlation (ρ)	−0.467	—	0.0006*

**Statistically significant at $p < 0.05$. df = degrees of freedom; ρ = Spearman's rank correlation coefficient.*

3.5 Age Distribution and Biomarker Comparison

The age distribution demonstrated a unimodal pattern centered around the sixth decade (mean 59.0 ± 12.8 years), consistent with the well-established postmenopausal predominance of endometrial adenocarcinoma (Fig. 7A). A grouped bar chart (Fig. 7B) provides a comparative overview of Ki-67 and PTEN expression level distributions across all categories, clearly illustrating the contrasting directionality of the two biomarkers in the study cohort.

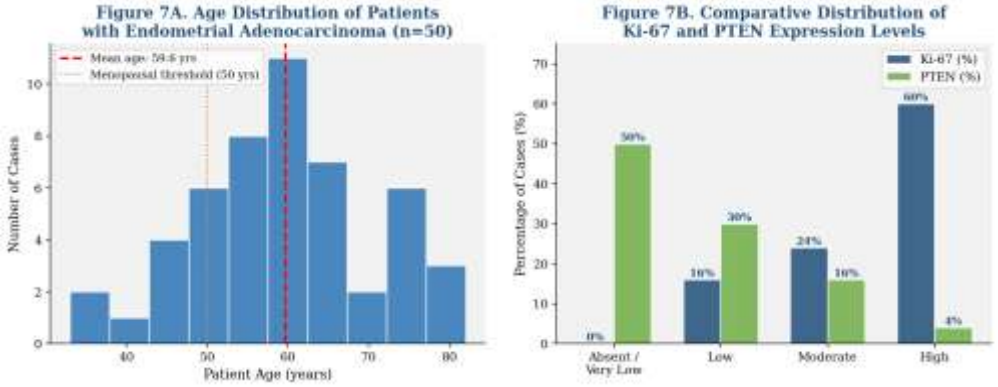

Fig. 7. (A) Histogram of patient age distribution in the study cohort (n = 50). The dashed red line indicates the mean age (59.0 years); the dotted orange line marks the conventional menopausal threshold (50 years). (B) Grouped bar chart comparing the percentage distribution of Ki-67 (blue) and PTEN (green) expression levels, illustrating their contrasting profiles across the expression spectrum.

3.6 Histopathological and Immunohistochemical Photomicrographs

Representative H&E photomicrographs (Fig. 1) demonstrate the spectrum of endometrial adenocarcinoma morphology in the study cohort, including variable architectural complexity, endometrioid and papillary serous patterns, squamous differentiation, and prominent nuclear atypia. Immunohistochemical photomicrographs (Fig. 2) confirm strong nuclear Ki-67 positivity in high-grade tumors (panels A–B) and complete PTEN cytoplasmic loss (panels C–D), with preserved stromal immunoreactivity serving as an internal positive control.

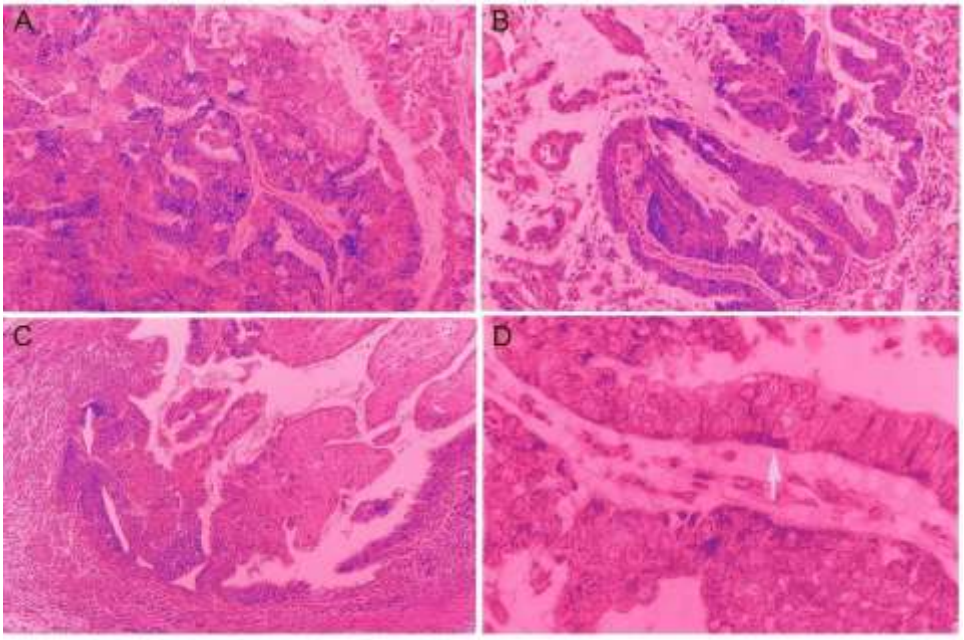

Fig. 1. Representative H&E photomicrographs of endometrial adenocarcinoma: (A) Endometrioid type with complex glandular architecture; (B) Papillary serous adenocarcinoma; (C) Squamous differentiation; (D) Subnuclear vacuolation with nuclear atypia. Original magnifications ×100 and ×200.

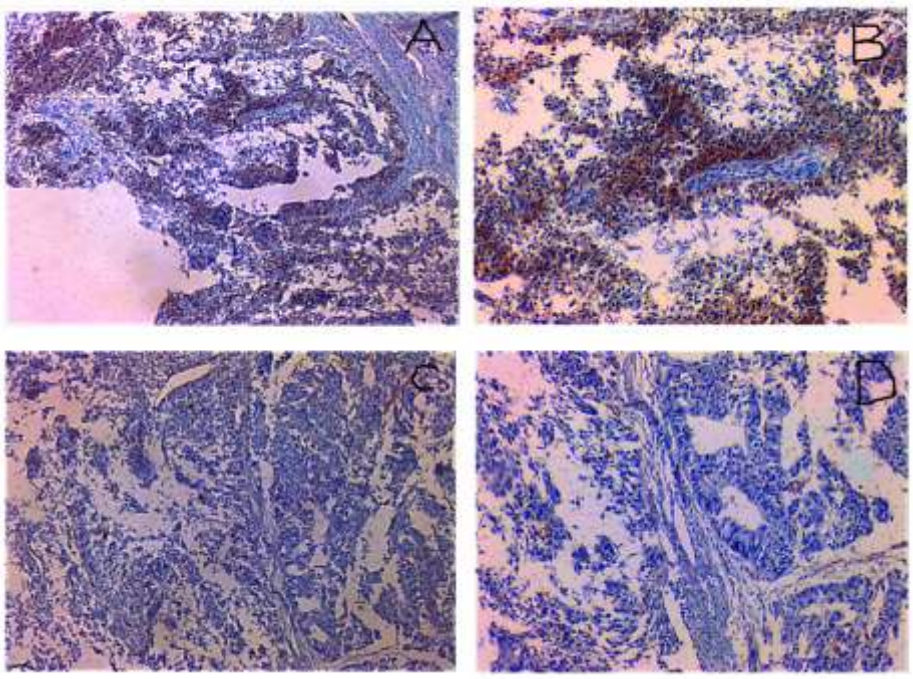

Fig. 2. Immunohistochemical photomicrographs: (A) Strong nuclear Ki-67 positivity in high-grade tumor cells (×100); (B) High-magnification view of Ki-67 nuclear staining (×200); (C) Complete PTEN cytoplasmic loss in tumor cells; (D) PTEN-negative tumor cells with retention of stromal immunoreactivity as internal positive control. DAB chromogen; hematoxylin counterstain.

Discussion

4.1 Overview of Findings

The current research confirms the high prevalence and prognostic value of Ki-67 overexpression and PTEN loss in endometrial adenocarcinoma, and proves that there is a statistically significant negative correlation between the two biomarkers (Spearman 0.467, 0.0006; 829.1 0.0065). These findings are in line with the biological complementation of Ki-67 being a proliferation marker and PTEN being a tumor suppressor that is active on PI3K/AKT/mTOR axis. Mechanistic basis of this association is shown in Fig. 8: PTEN phosphatase inhibition leads to constitutive phosphorylation of AKT, which causes the increase of the cyclin D1 and CDK4/6 complexes and a decrease in the CDK inhibitor p27, which in turn allows the entry into S-phase without restriction which is directly reflected in greater nuclear Ki-67 staining.

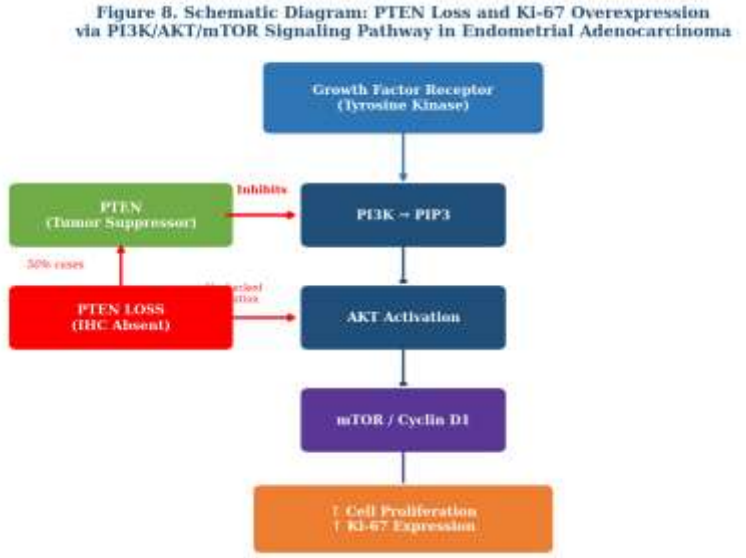

Fig. 8. Schematic pathway diagram illustrating the mechanistic basis for the inverse correlation between PTEN loss and Ki-67 overexpression in endometrial adenocarcinoma. Loss of PTEN phosphatase activity leads to constitutive PI3K/AKT/mTOR activation, enhanced cyclin D1-mediated cell cycle progression through CDK4/6, downregulation of p27, and resultant elevation of Ki-67 nuclear staining as a direct measure of proliferative activity.

4.2 Ki-67 as a Marker of Proliferative Activity

The level of Ki-67 labeling index was in the range of 8 percent to 92 percent with 60 percent showing a high level of expression (>51 percent). The positive rise in the mean of Ki-67 LI with the tumor grades (28.5 in Grade 1, 55.3 in Grade 2, and 74.2 in Grade 3) is in line with the available literature. Kitson et al. (2018) in a large-scale series have shown high Ki-67 LI as an independent predictor of poor disease-free and overall survival in endometrial carcinoma regardless of FIGO stage. The same results have been described by Urruticoechea et al. (2005), who suggested Ki-67 as an independent prognostic variable in small-size disease that could also be used as a selection criterion in candidates of adjuvant therapy despite having low-risk clinicopathological characteristics.

Though the Chi-square test in the current study has failed to achieve the statistical significance of the relationship between the variables grade and Ki-67 (2 = 5.98, p = 0.426), the seemingly nonsignificant directional relationship between the two variables (Spearman 0.276, p = 0.053) and the apparent biological gradient across the grades indicates that there is in fact an underlying relationship. The insignificance of

the statistical results is probably because of low statistical power due to the sample size (n = 50) and not because of the non-existence of the real biological correlation. This grade-related Ki-67 gradient needs to be validated with sufficiently powered cohorts of study in the future.

4.3 PTEN Loss: Frequency, Mechanisms, and Epigenetic Regulation

The current series established a loss of PTEN (absent or low IRS-loss) in 80% and total immunohistochemical loss in 50% of cases. They are within the ranges that have been reported in the molecular epidemiology of endometrioid adenocarcinoma, where somatic PTEN inactivation, most frequently by mutation, allelic deletion, promoter methylation, or post-translation degradation, has been reported in 4083% cases (Zhao et al., 2013; Pallares et al., 2005). Pallares et al. (2005) affirmed that immunohistochemical PTEN loss is not only an efficient and cost-effective surrogate of underlying molecular inactivation but also an effective and feasible method of clinical risk stratification in resource-limited population.

The roles of epigenetic mechanisms in silencing the PTEN and the overall disruption of the tumor suppressor networks seem to be central in the process of endometrial carcinogenesis. It was found that Al-Deresawi et al. (2018) compared the SOX4 and miR-203 expression of SOX4 in endometrial adenocarcinoma with normal controls means that SOX4 expression increased significantly (9.24 ± 0.52-fold, p = 0.01), whereas the miR-203 expression decreased significantly (0.073 ± 0.02-fold, p = 0.01). These results are mechanistically relevant to the present study: similarly to the miR-203 hypermethylation being the means of releasing SOX4 under post-transcriptional repression, other regulatory non-coding RNAs can undergo an epigenetic silencing in PTEN-deficient tumors, playing a role in the boosting of pro-proliferative signals.

A role in endometrial tumorigenesis early in time and PTEN inactivation was established by Al-Kinani and Al-Badri (2025), who found simultaneous PTEN loss and high Ki-67 levels in the atypical endometrial hyperplasia (endometrial intraepithelial neoplasia, EIN) - a known obligatory precursor lesion. This time precedence contributes to the categorization of PTEN inactivation as an initiating, but not secondary event in the hyperplasia-to-carcinoma process, irrespective of the molecular pathway concerned.

4.4 Inverse Correlation Between Ki-67 and PTEN: Mechanistic and Clinical Implications

The main conclusion of the current research is the significant inverse relationship between the expression of Ki-67 and PTEN (1= -0.467, p=0.0006). Table 4 (Fig. 6) shows that the total PTEN loss was observed in 66.7 percent of the high-Ki-67 cases, but low-Ki-67 cases were mainly linked to the moderate-to-high expression of PTEN. This is a mechanistically consistent relationship: working PTEN phosphatase activity transforms PIP3 into PIP2, which in turn prevents AKT phosphorylation and downstream pro-proliferative cascades. On the other hand, the inactivation of PTEN leads to constitutive activation of AKT that stimulates/ enhances retinoblastoma protein (pRb) phosphorylation through the upregulation of cyclin D1/ CDK4, releasing E2F transcription factors and committing cells to proceed to S-phase - direct measurements of which are quantified by Ki-67 nuclear staining.

Translational wise the Ki-67 and PTEN joint assessment is more informative than both Ki-67 and PTEN assessments alone, as validated by the meta-analyses of Cappelli et al. (2021) and Erkanli et al. (2007). Status-PTEN status correlates with PI3K inhibitor responsiveness, mTOR inhibitor responsiveness (everolimus, temsirolimus) and AKT inhibitor responsiveness, which are undergoing clinical trials in endometrial carcinoma (Liu et al., 2022). A high Ki-67 expression, in its turn, can help to designate the

candidates to cell cycle-targeted therapy, including cell cycle 4/6 inhibitors like palbociclib and ribociclib. Combination of the two biomarkers - which may be complemented by the use of epigenetic markers like miR-203 methylation status (Al-Deresawi et al., 2018) - into therapeutic decision-making algorithms have a significant potential of personalized management approaches.

4.5 Limitations

There are a number of limitations that should be noted. The retrospective and single-centre design and the moderate sample size (n = 50) decrease the statistical power and restrict the generalizability. Although the immunohistochemistry has proven its utility and is cost-effective, it fails to detect all PTEN-inactivating mechanisms, such as promoter methylation, silencing by microRNA (e.g. miR-203 Al-Deresawi et al., 2018) or by proteasomal degradation; combination of bisulfite sequencing, quantitative MSP or next-generation sequencing would provide a more global molecular characterization. Also, no long-term following data were available, making it impossible to directly correlate the profiles of biomarkers with disease-free or overall survival outcomes. The present findings should be confirmed and extended through future prospective multicenter studies with a long follow-up and molecular profiling.

Conclusion

Ki-67 and PTEN are useful and correlated immunohistochemical biomarkers to the evaluation of tumor aggressiveness in endometrial adenocarcinoma. Their considerable negative correlation is immunohistochemical evidence of deregulation of the PI3K/AKT/mTOR pathway that is a result of PTEN inactivation. Combining the two biomarkers as a part of the standard diagnostic assessment of endometrial adenocarcinoma can enhance the risk stratification of the prognosis and contribute to the individual selection of the therapeutic approach. The larger multicenter prospective studies should be strongly encouraged as a way of validation.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board of the University of Sumer / Al-Karamah Teaching Hospital, Wasit Province, Iraq (Approval No.: 198587-2025). All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki (revised 2013).

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

M.J.H. Al-Kinani: Conceived and designed the study, performed immunohistochemical analysis, and wrote the manuscript. N.H.S. Al-Shabbani: Performed histopathological examination and scoring, and critically revised the manuscript. I.A. Fahad: Supervised clinical data collection and contributed to manuscript revision. All authors read and approved the final manuscript.

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